UNITED STATES PATENT AND TRADEMARK OFFICE

C/C

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,936	06/24/2003	Charles Jack Fisher	X12448B	1851

25885 7590 06/15/2005

ELI LILLY AND COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/602,936	FISHER ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,22,25-30 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21, 22, 25-30, 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The Amendment filed 3/17/05 has been entered. Claims 23, 24, 31, and 32 have been cancelled and Claims 37 and 38 have been added. Claims 21-22, 25-30, and 33-38 are pending and have been considered in this Office Action.

Rejections Withdrawn

The rejection of Claims 22, 25, 27, 30, 33, and 35 under 35 U.S.C. 112, first paragraph as containing new matter is withdrawn in light of the amendment to the claims.

The rejection of Claims 26-28 and 34-36 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in light of the amendment.

Rejections Maintained

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 21, 22, 25-28, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glas-Greenwalt et al. (J. Lab. Clin. Med. (1986) 108: 415-422; ref. CI of IDS filed 6/24/03) and Gruber et al. (Circulation (1990) 82: 578-585; ref. CH of IDS filed 6/24/03) and Foster et al. (U.S. Patent No. 5,516,650; ref. AB of IDS filed 6/24/03).

Applicants argue that neither the teachings of the prior art, the nature of the problem to be solved, nor the knowledge of one skilled in the art provides motivation to combine the references because Greenwalt et al. does not teach recombinant human protein C or its use in treating TTP and thus provides no motivation to combine with Gruber et al. and Foster et al. which collectively are concerned with recombinant protein C and aPC. This argument has been considered but is not deemed persuasive for the reasons provided in the previous Office Action at pp. 4-7. In summary of that action, Glas-Greenwalt et al. teaches that patients with TTP have a protein C deficiency which can be normalized by plasma exchange (plasma contains protein C). Therefore, combined with the teaching of Gruber et al. that recombinant activated protein C can be used successfully to treat platelet dependent thrombus formation in a model of arterial thrombosis (TTP is characterized by widespread arterial thrombosis), it would have been obvious to one of ordinary skill in the art to develop a method of treatment for TTP using recombinant human aPC.

Applicants argue that Glas-Greenwalt et al. discloses protein C levels without any discussion of aPC or knowledge of whether the microvasculature of patients with TTP can support the conversion of protein C to aPC. This argument has been considered but is not deemed persuasive because it only adds strength to the argument that in light of Gruber et al. and Glas-Greenwalt et al., one of ordinary skill would be motivated to administer aPC in the treatment of TTP. First, Glas-Greenwalt et al. reports a deficiency in protein C in patients with TTP. It follows that a deficiency of protein C (the precursor of aPC) would also mean a deficiency of aPC. Second, as Applicants admit

and as one of ordinary skill would recognize, the plasma exchange as used in Glas-Greenwalt et al. would provide aPC. Third, one of ordinary skill in the art would recognize the desirability of administering activated protein C because, as explained in Foster, it would remove the need to activate the protein in vivo (Col. 7, lines 45-47). Thus, combined with the teaching of Gruber et al.. that recombinant activated protein C can be used successfully to treat platelet dependent thrombus formation in a model of arterial thrombosis (TTP is characterized by widespread arterial thrombosis), it would have been obvious to one of ordinary skill in the art to develop a method of treatment for TTP using recombinant human aPC.

Applicants argue that Glas-Greenwalt et al. indicates that beneficial treatment of TTP will include fibrinolytic activity whereas Gruber et al. summarizes that infusion of APC failed to demonstrate induction of fibrinolysis. Applicants further argue that Gruber et al. does not support the profibrinolytic property of aPC which is useful in treating TTP. Thus, applicants argue, one of skill in the art would not be motivated to combine or have any expectation of success in combining Gras-Greenwalt et al. and Gruber et al. from the aspect of the therapeutic need for fibrinolytic activity in the treatment of TTP. This argument has been considered but is not deemed persuasive for the following reasons. Glas-Greenwalt et al. suggests that beneficial treatment of TTP would include reversal of fibrinolytic and protein C abnormalities (p. 421, Col. 1, 1st paragraph). Glas-Greenwalt et al. teaches that protein C levels are deficient in TTP (p. 416, last line of second paragraph). Gruber et al. teaches that aPC can be used to treat arterial thrombosis, a problem in TTP. Thus, one of skill in the art would be motivated to use

aPC in the treatment of TTP from the teachings and suggestions of Glas-Greenwalt et al. (that protein C levels are deficient and that reversal of this deficiency could be beneficial in the treatment of TTP) and Gruber et al. (that aPC can be used successfully to treat arterial thrombosis (a problem in TTP)).

Applicants argue that Foster et al. does not disclose or suggest use of human protein C or human aPC in the treatment of TTP and that Foster et al. indicates that aPC can be used as an anticoagulant and not for its profibrinolytic properties. Foster et al. shows that recombinant protein C was readily available at the time of the invention and that it is preferable to use recombinant and activated recombinant PC over PC isolated from plasma. Moreover, Foster et al. states that "in view of the clinical applicability of human protein C and human activated protein C in the treatment of thrombotic disorders" (which would encompass TTP and HUS), "the production of useful quantities of human protein C and human activated protein C by recombinant DNA techniques is clearly invaluable" (Col. 2, lines 45-50).

Applicants argue that the combination of references fails to provide a reasonable expectation of success. Applicant argues that Glas-Greenwalt et al. teaches that not all of the patients with TTP had low protein C levels. This argument has been considered but is not deemed persuasive because Glas-Greenwalt et al. concludes that the patients with TTP had a deficiency in protein C (see p. 416, Col. 1, last line of second paragraph; p. 420, Col. 1, last sentence of 2nd paragraph) and suggests that reversal of this protein C deficiency might be beneficial in the treatment of TTP (p. 421, Col. 1, 1st paragraph). Thus, with these teachings combined with the observation of Glas-

Greenwalt et al. that plasma exchange (containing aPC) therapy resulted in temporary reversal of TTP abnormalities and the teachings of Gruber et al. that rAPC inhibited thrombus formation in a model of arterial thrombosis, one of ordinary skill would have had a reasonable expectation of success in treating TTP with protein C. Applicants' argument that Glas-Greenwalt et al. does not teach or suggest that protein C alone may be of therapeutic value in treating TTP is not persuasive because the claims are not limited to using protein C alone in the treatment of TTP.

Applicants also argue that Gruber et al. teaches administration of aPC at a dose that is higher than the present invention. This argument has been considered but is not deemed persuasive. First, Applicants are arguing as if each reference used in the obviousness rejection must teach each and every limitation of the instant claims. Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As explained in the previous Office Action, based on the results using a primate model, it was well within the skill of the ordinary artisan at the time of the invention to take the results of Gruber et al. using the primate model and the observations of Glas-Greenwalt et al. and adjust the dosages such that they would apply to humans. Moreover, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. " In re Aller, 105 USPQ 233, 235 (CCPA 1955) (as cited in MPEP 2144.05 II). This argument and the previous rejection are applied to new Claim 37

which defines the dosage of aPC administered in the claimed method. The examiner notes that the routine nature of optimizing effective dosages and administration regimens is admitted in the present Specification (p. 8, lines 23-30).

Therefore, upon review of all three references as a whole, it appears that TTP (as well as HUS) are conditions that arise due to the formation of thrombi in peripheral arterioles leading to widespread occlusion of blood vessels. Gruber et al. teaches that recombinant protein C can be used successfully to treat platelet dependent thrombus formation in a model of arterial thrombosis. TTP is characterized by widespread arterial thrombosis wherein the microthrombi are rich in platelets and Glas-Greenwalt et al. teaches that patients with TTP have a protein C deficiency which can be normalized by plasma exchange. Therefore, it would have been obvious to one or ordinary skill in the art at the time of the invention, to combine the teachings of Glas-Greenwalt et al. with that of Gruber et al. and Foster et al. to develop a method of treatment for TTP using recombinant human PC. Gruber et al. and Foster et al teach that one would be motivated to do this in order to develop and use PC as an antithrombotic agent to treat septic shock and stroke which are final manifestations of TTP. The highly encouraging teachings of Gruber et al. using an arterial thrombosis model would have motivated one of ordinary skill in the art to extend the same to humans with the appropriate dosage and infusion methods. One of ordinary skill in the art would also be motivated to develop and use a recombinant PC to avoid problems with the short supply of plasma and avoid contamination of the final product with potential pathogens. One of ordinary skill in the art would have had a reasonable expectation of success since Glas-

Greenwalt et al. teach that PC antigen levels were low in TTP patients and that plasma (containing PC) exchange therapy resulted in temporary reversal of TTP abnormalities and Gruber et al. teach that recombinant activated PC inhibited thrombus formation in a model of arterial thrombosis.

Claims 29-30, 33-36, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glas-Greenwalt et al., Gruber et al., and Foster et al. as applied to claims 21-28 above, and further in view of Hollenbeck et al. (Nephrol. Dial. Transplant. (1998) 13: 76-81; ref. CF in IDS filed 6/24/03).

Applicants argue that while Hollenbeck et al. teach that plasma exchange provides therapeutic value, Hollenbeck et al. do not mention any of the factors addressed by Glas-Greenwalt et al. and that one of skill in the art would not have motivation to combine Hollenbeck et al. and Glas-Greenwalt et al. with Gruber et al. and Foster et al. for the reasons cited in the rejection above. This argument has been considered but is not deemed persuasive for the reasons provided above and below.

Applicants argue that at the time of the invention the mechanisms of how plasma infusion and exchange successfully treated HUS were unknown and anticoagulants had not been shown to be of benefit. Thus, one of skill in the art would not have had a reasonable expectation of success in treating HUS by combining Hollenbeck et al. and Gruber et al. and Foster et al. This argument has been considered but is not deemed persuasive because Hollenbeck et al. shows that the relation between TTP and HUS is that they are one and the same occurring in different individuals. It would have been

obvious to one of ordinary skill in the art to extend the results of Gruber et al. combined with the teachings of Glas-Greenwalt et al. and Foster et al. for use in HUS as Hollenbeck et al. teaches that HUS and TTP are identical disorders.

Applicant again applies the argument that the references do not teach the dosages and treatment regimen of the present Claims. This argument is not deemed persuasive. First, Applicants are arguing as if each reference used in the obviousness rejection must teach each and every limitation of the instant claims. Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As explained in the previous Office Action, based on the results using a primate model, it was well within the skill of the ordinary artisan at the time of the invention to take the results of Gruber et al. using the primate model and the observations of Glas-Greenwalt et al. and adjust the dosages such that they would apply to humans. Moreover, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. " In re Aller, 105 USPQ 233, 235 (CCPA 1955) (as cited in MPEP 2144.05 II). The examiner notes that the routine nature of optimizing effective dosages and administration regimens is admitted in the present Specification (p. 8, lines 23-30). It is noted that new Claim 38 has been added to the rejection for the reasons cited in the previous Office Action and above since it defines the dosage of aPC administered in the method.

Therefore, in view of the combined references of Glas-Greenwalt et al., Gruber et al., Foster et al.,and Hollenbeck et al., it would have been obvious to one of ordinary skill in the art to develop a method of treating HUS using recombinant protein C and recombinant activated protein C. While Hollenbeck et al. does not provide the dosages or steps of the method, given the close relationship between HUS and TTP and success in using protein C to treat thrombus formation disclosed in Gruber et al., it would have been well within the skill of the art to empirically set up dosages and safe methods of infusion for treatment of HUS. Moreover, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (as cited in MPEP 2144.05 II). One of ordinary skill in the art would have been motivated to do so in order to treat two closely related abnormalities such as TTP and HUS with a single agent. One of ordinary skill in the art would have had a reasonable expectation of success since Gruber et al. show promising results in using recombinant protein C to treat thrombus formation in an arterial thrombosis model.

Conclusions

No Claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
June 8, 2005

ROBERT A. WAX
PRIMARY EXAMINER
Art Unit 1653